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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,198	06/04/2001	Jens Chr. Jensenius	09011-002002	2556

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	15

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/874,198	JENSENIUS ET AL.	
	Examin r	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,11,22,28 and 41-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4, 5 and 46* is/are allowed.

6)☒ Claim(s) *6,11,22,28,41-45 and 47-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

Applicant's Amendment C, Paper No. 14 filed May 28, 2003, has been entered and claims 1-3, 7-10, 40 and 56 were cancelled at Applicant's request, rendering the rejections of record of these claims moot but creating an issue of claim dependency for claims 22 and 28 which now depend from a cancelled claim. Entry of the amendments to claims 11, 41-45, 47 and 55 submitted with Paper No. 14 does not free claims 41-45, 47 and 55 from rejections of record under 35 U.S.C. §112, first paragraph, but requires that claim 11 now be included in rejections under 35 U.S.C. §112, first and second paragraphs. This communication is not made final because claims 6 and 41-45 could have been included in the rejections of record under the first paragraph of 35 U.S.C. §112 stated in Paper No. 12 mailed January 28, 2003, and they are now included in these rejections of record. Claims 41-45, 48 and 54 are also rejected under 35 U.S.C. §101 because no claim specifically requires that a claimed polypeptide include an integral peptide region of a human MASP-2 polypeptide demonstrated to be useful in raising antisera that may specifically recognize and detect a MBL/MASP-2 complex.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6, 11, 22, 28, 41-45, and 47-55 are rejected under 35 U.S.C. §101 because the claimed invention lacks patentable utility.

This is a new ground of rejection because it now includes claims 6, 41-45 and 47-55. Claim 11 is included in this rejection in view of Applicant's amendment of Paper No. 14. Applicant's arguments filed May 28, 2003, have been fully considered but they are moot because the subject matters of claims 22 and 28 are now indefinite and might describe a peptide of SEQ ID NO:1, or a mature MASP-2 protease of SEQ ID NO:2, or even a

member of any of the genera of variants of claims 41-45, 48 and 54. The Declaration under 37 CFR 1.132 of the co-inventors, Professors Jensenius and Thiel, is considered to be persuasive in establishing the utility of pharmaceutical compositions that comprise the mature MASP-2 protease having the amino acid sequence set forth in SEQ ID NO:2 and methods for treating patients with the composition. This is because the artisan would be aware, upon reading the specification, of the substrate of the MASP-2 protease and that the locus of activity of a MASP-2 protease is the blood, wherein the Declaration of the co-inventors establishes that administration of a pharmaceutical composition comprising the MASP-2 protease permits the therapeutic management of a medical condition involving a decrease in MASP-2 activity in the circulatory system. If claims 22 and 28 were instead construed to describe a pharmaceutical composition comprising, e.g., the amino-terminal peptide region of the MASP-2 protease set forth in SEQ ID NO:1, as well as methods for treating patients with the composition, neither the Declaration nor the instant specification could support such an *in vivo* utility, because the Declaration of the co-inventors does not address this issue and the specification fails to support an *in vitro* utility for compositions comprising the peptide region of the MASP-2 protease set forth in SEQ ID NO:1.

Similarly, the specification provides no credible utility for the undisclosed polypeptides described by claims 6, 41-45, and 47-55 because the claims do not require the retention of any particular disclosed, integral and antigenic, region of the MASP-2 protease having the amino acid sequence of SEQ ID NO:2. Mere allegations of a prospective, potential, utility for the undisclosed polypeptides do not rise to the level of a credible assertion of a specific, substantial, *in vitro* or *in vivo* utility. A method of use of a material for further research to determine, e.g., its specific biological role, thus identifying or confirming a "real world" context for its use, cannot be considered to be a "substantial utility". *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). There is no indication that

peptides having an amino acid sequence of SEQ ID NO:1 are useful in pharmaceutical compositions or in methods of treatment, nor any indication that undisclosed products of claims 41-45, 48 and 54 have any specific utility where they fail to require any specific regions of the amino acid sequence of SEQ ID NO:2 be included therein, permitting an immediate use by the public.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 22, 28, 41-45, and 47-55 are also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 6, 11, 22, 28, 41-45 and 47-55 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new ground of rejection because it now includes claims 41-45. Claim 11 is included in this rejection in view of the amendment of Paper No. 14. Claim 6 is drawn to any polypeptide that has a specific mass, 52 kilodaltons [kDa], and that comprises a disclosed 20 kDa peptide comprising the 39 amino acid-sequence of SEQ ID NO:1. The specification, however, describes only one polypeptide that has both characteristics, the heavy chain of the mature MASP-2 protease having the amino acid sequence set forth in SEQ ID NO:2. While the specification permits the artisan to identify the portion of the amino acid sequence of SEQ ID NO:2 that constitutes the non-catalytic, amino-proximal, heavy region of the MASP-2 product, it nowhere provides identifying characteristics of any other product that differs in that region of its amino acid sequence contributing the major

portion of its 52 kDa mass from the disclosed MASP-2 heavy chain region of SEQ ID NO:2. The specification also fails to exemplify or describe the preparation of members of the genera of polypeptides comprising unspecified arrays of 20 amino acids drawn from anywhere within the amino acid sequence of SEQ ID NO:2 according to claim 41, or members of genera of polypeptides comprising unspecified arrays of 25, 35, 50, or 100 amino acids abstracted from anywhere within the amino acid sequence of SEQ ID NO:2 according to claims 42-45. The specification suggests only a limited array of amino acids, the sequence set forth in SEQ ID NO:1, that might be incorporated in an heterologous polypeptide but none of claims 6 and 41-43 are drawn to a fusion polypeptide.

No polypeptide disclosed by the specification can have both characteristics of claim 11, a mass of 52 kDa and the entire amino acid sequence of SEQ ID NO:2, because these characteristics are mutually exclusive. Neither the specification nor recitations of claims 47-55 provide an adequate written description of the subject matters of a variant MASP-2 product that has generic serine protease activity or the more specific activity required for *in vitro* assays for MBLEctin complement pathway. Nor does the specification provide an adequate written description of variants that exhibit a mannan-binding lectin associating activity. The specification cannot identify or suggest any set of six amino acid positions within the amino acid sequence of SEQ ID NO:2 wherein an amino acid sequence modification should be made, according to claim 52, or the nature of any modifications at any set of amino acid positions. Where the artisan reading the specification cannot ascertain the nature of any claimed, but undisclosed, species of claims 6, 11, 22, 28, 41-45 and 47-55, the artisan could not recognize that Applicant was in possession of these subject matters at the time the specification was filed. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first

paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of a protease that diverges at as many as six amino acid positions from the sequence of SEQ ID NO:2, or of a peptide product that diverges at as many as six amino acid positions from the sequence of SEQ ID NO:1, neither does it provide any characteristic permitting correlation between undisclosed structures of any protein product among the myriad species of generic proteins of claims 6, 11, 22, 28, 41-45 and 47-55 and the disclosed amino acid sequences of SEQ IDs NOs:1 and 2.

Applicant's arguments filed May 28, 2003, have been fully considered but they are not persuasive. Applicant argues at pages 3-4 of Paper No. 14 that SEQ ID NO:1 comprises an "active site". It does not. The active site of the MASP-2 protease is, see Figure No. 2, disclosed to be present in the light chain of the protease, entirely distinct from the amino terminal peptide region of the mature product set forth in SEQ ID NO:1 and distinct as well from the 52 kDa heavy chain region of the mature product. There is no Example 13 in the specification and SEQ ID NO:3 is a nucleotide sequence encoding the MASP-2 precursor, which comprises an further, amino-terminal, signal peptide amino-proximal to the peptide region of SEQ ID NO:1. Whatever Applicant may have intended to argue, the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, claims 6, 11, 22, 28, 41-45 and 47-55 rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace other, as yet unknown, mammalian proteases. Applicant declines in Paper No.

14 to address the relevant decisional law concerning claims describing undisclosed genera of products such claims 6, 11, 22, 28, 41-45 and 47-55 herein and is invited to do so in response to this communication. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of the undisclosed generic proteins reached by the claims rejected herein to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant fields of molecular biology and medicine could not predict the structure, or other properties, of the generic products of claims 6, 11, 22, 28, 41-45 and 47-55, or the nature of the pharmaceutical composition of claim 22 that might comprise any of these generic products or a method of treatment of claim28 using such a generic product.

Claims 6, 11, 22, 28, 41-45 and 47-55 are rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for any embodiment of an inhibitory product, for any embodiment of a method of treatment using a disclosed protease, nor for the preparation of a functioning human MASP-2 protease having an amino acid sequence that diverges from the amino acid sequence of SEQ ID NO:2, nor for a product that diverges as much as 15% from the amino acid sequence of SEQ ID NO:1 that has any use in identifying a native, human, MBL-MASP-2 complex. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

This is a new ground of rejection because it now includes claims 41-45. Claim 11 is included in this rejection in view of Applicant's amendment of Paper No. 14. Applicant's arguments filed May 28, 2003, have been fully considered but they are not persuasive. Applicant argues at pages 4-5 of Paper No. 14 that "conserved residues may . . . be identified by aligning MASP-2 sequences", perhaps suggesting to the artisan both sites and substituents for conservative substitutions. Claims 6, 11, 22, 28, 41-45 and 47-55 are not enabled because claim 11 describes a physical impossibility because the generic claims

6, 22, 28, and 41-45 contemplate, see page 28, lines 8-19, of the specification arbitrary assignments of any or all of amino acid substitutions, additions or deletions in the sequence of the disclosed, native, human MASP-2 protease of SEQ ID NO:2, or its internal peptide of SEQ ID NO:1, in undisclosed regions of the amino acid sequence, because claims 47-52 and 55 contemplate arbitrary assignments of any or all of amino acid substitutions, additions or deletions in the sequence of the disclosed, native, human MASP-2 protease, because claims 53 and 54 contemplate substitutions of amino acids at arbitrarily assigned locations, and because neither the specification nor the prior art of record, taken together, can support the introduction of conservative substitutions at as many as 103 unspecified amino acid positions in the 686-amino acid sequence of the mature MASP-2 protease yet produce a variant that retains either a native protease or a mannan-binding lectin-associating activity.

At pages 4-5 of Paper No. 14, Applicant argues that artisans seeking to practice the invention of claims 47-55 might select analogous positions for conservative substitution by referring to other, related, serine proteases. Yet a Federal Circuit panel, when considering whether or not definitional statements can enable a scope argued to extend beyond the native amino acid sequence disclosed for a protease to embrace a specific variant protease encoded by a specifically-altered DNA sequence, held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 1564-65, 31 USPQ2d 1161, 1168 (Fed. Cir. 1994). Applicant cannot point to any members of the class of proteases having amino acid sequences related to SEQ ID NO:2 wherein as many as six amino acids have specifically been identified for concurrent modification and Applicant's specification cannot identify six amino acids within the sequences of human

MASP-2-related proteases – such as the prior art MASP-1, C1 and C1q – that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to function as a protease. Mere sequence perturbation cannot enable the design and preparation of a myriad of divergent proteases that will provide the public with a protease that retains its native functions.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit has approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Applying the *"Forman"* factors discussed in *Wands, supra*, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequences of products of SEQ IDs NOs:1 and 2 to the extent recited in the claims,

b) the specification lacks working examples wherein products of SEQ IDs NOs:1 and 2 are altered to the extent recited in the claims,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of human products having amino acid sequences related to SEQ IDs NOs:1 and 2 have had as many as six amino acids specifically identified for concurrent modification.

Thus the scope of subject matters embraced by claims 6, 11, 22, 28, 41-45 and 47-55 is unsupported by the present specification.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 11, 22, and 28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite in commencing with the definite article, "The", because the rest of its recitation does not indicate that any particular polypeptide has both the sequence of SEQ ID NO:1 and a mass that is over two-fold greater than the mass that can be predicted from the amino acid sequence of SEQ ID NO:1. Claim 11 is indefinite because the amino acid sequence of SEQ ID NO:2 has a calculated mass that far exceeds the mass limitation, 52 kDa, recited for the same polypeptide in the claim. Claims 22 and 28 are indefinite because they depend from claim 1, which has been canceled, thus the public cannot determine the subject matter which applicant regards as the invention.

Allowable Subject Matter

Claims 4, 5 and 46 are allowed because the publications made of record herewith do not disclose or suggest polypeptides having the amino acid sequences of either of SEQ IDs NOs:1 or 2, nor do they indicate that polypeptides having the amino acid sequences of either SEQ ID NO:1 or SEQ ID NO:2 were otherwise reported in any prior publication.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. The examiner's direct FAX telephone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
July 31, 2003

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